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THE STATE OF THE CARDIOVASCULAR SYSTEM OF ATHLETES FROM THE PERSPECTIVE OF MOLECULAR GENETICS

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ABSTRACT

The development of molecular genetics has made it possible to conduct promising molecular genetic studies, with the help of which it is possible to conduct clinical diagnostics of cardiovascular diseases that are inherited and have a genetic basis. This becomes especially important among the sports contingent, the use of modern genetic tests allows you to differentiate the "sports heart" from hereditary genetic diseases, and their use also allows you to eliminate possible risks with the necessary recommendations in the plans for preparing athletes for responsible competitions.

KEYWORDS: genes, hereditary diseases of the cardiovascular system, cardiomyopathy, sports heart, sudden cardiac death, molecular genetic tests.

Sports, especially at the professional level, can have life-threatening disorders of the cardiovascular system (CVS), which can lead to arrhythmia, sudden cardiac death (SCD), the cause of which is sometimes very difficult to determine[1] Most of all, the occurrence of these conditions may be associated with the presence of hereditary cardiovascular diseases (CVD), possibly not diagnosed in athletes in a timely manner[2,3,4], since the differential diagnosis of hereditary CVD among this contingent presents certain difficulties. This is primarily due to the functional activity of the CVS, as well as ongoing changes in electrical, structural and functional activity due to physiological adaptation to the resulting increased loads arising from regular active training processes. The result of these functional and structural changes is the formation of a "sports heart", which is difficult to differentiate with the development of cardiomyopathies and other diseases of the cardiovascular system that have a genetic basis.[1,5] In sports, accurate differential diagnosis is of particular relevance, the conduct of which will prevent cases of sudden death, as well as disqualification of athletes. To this end, a molecular genetic study can now be a confirmatory aid to the hereditary nature of CVD, with the help of which it is possible to determine any genetic defect that caused CV pathology. The negative aspect of this study is insufficient knowledge about the genetic background of CVD associated with heredity, which entails an unsatisfactory test result, which may be due to the presence of mutations in genes that are not yet known, but they may be closely related to hereditary heart pathology.[6,7]

The identification of various genetic modifications can contribute to the determination of an incorrect diagnosis of the disease as a result of the presence of heterogeneous phenotypic signs.[8]

Recommendations for the use of molecular genetic studies. According to the literature data, molecular genetic tests can be recommended in patients with hereditary CVD, the purpose of which is to determine the genetic background of the disease.[6,7] Testing can also be recommended to identify patients at the preclinical stage of the disease and confirm the presence of genetic risks.[6,7,9] In the sports contingent with the presence of borderline changes during molecular genetic testing, it is possible to carry out differential diagnostics of pathological changes with physiological adaptive processes, remodeling of the heart, determined during active sports activity. The emerging structural and neurovegetative changes, hypertrophy and dilatation of the ventricles associated with borderline systolic dysfunction, hypertrabeculation, prolongation of the QT interval, early repolarization, inversion of the anterior T wave and blockade of the right leg of the Gis bundle are difficult in differential diagnostic terms.

Among the sports contingent who may have hereditary CVD, it is important to send them to cardiology centers for observation with the inclusion of cardiologists,

geneticists, sports doctors for clinical diagnosis, correct interpretation of genetic diagnosis, management and clinical support of athletes, followed by a decision on their admission to classes.[9]

Molecular genetic tests in the sports contingent. Tests are carried out when a genetic disease is suspected, followed by the athlete's referral to a specialized cardiology center, in which, under the supervision of sports doctors, a sports cardiologist, the necessary CVS examinations must be carried out with mandatory molecular genetic testing.[10,11,12,13] The sports contingent, if suspected of a genetic heart disease, requires careful collection of anamnesis with careful study of the complaints and symptoms presented: the occurrence of fainting, sharp chest pain, palpitations, especially during physical exertion, family history of the presence of genetic CVD.[10,11,12,14,15,16] Sometimes athletes can hide the presence of these symptoms, as they are afraid of disqualification and suspension from sports activities. Among athletes, carrying out and detecting CVD genetic diseases at early stages can reduce the risks of SCD[17], which is especially important, since active training causes and accelerates the occurrence of diseases and life-threatening rhythm disturbances, for example: arrhythmogenic cardiomyopathy (ACM), in which intense physical exertion worsens the phenotype of the disease with an increase in the risk of ventricular arrhythmias and heart failure.[18] In the presence of hypertrophic cardiomyopathy (HTCM), intensive training can lead to hypertrophy of the left ventricle (LV) caused by physical exertion, followed by the development of ischemic phenomena in the myocardium, cell death and myocardial replacement with fibrous tissue, leading to electrical instability of the ventricle.[2,19] In Marfan syndrome, hemodynamic load on the aorta due to increased blood pressure and shock volume during intense physical activity can increase the rate of aortic dilation, increasing the risk of aortic rupture.[20] The diagnostic value of testing ranges from 20%, with Brugada syndrome (BrS) to 85%, with long QT syndrome.

Hereditary diseases of the CVS.

One of the most frequently diagnosed diseases with a genetic basis is hypertrophic cardiomyopathy (HTCM), an autosomal dominant hereditary disease characterized by an unexplained maximum wall thickness of the left ventricle (LV) ≥15mm or ≥13mm with a family history of HTCM, a positive response of a molecular genetic test.[21,22] According to the literature, the maximum wall thickness does not exceed 12mm in women and 13mm in men of the Caucasian race, 13mm in women and 16mm in men of Afro-Caribbean athletes associated with increased LV cavity size.[19,23,24,25] It should be noted that for elite athletes, an increase in the thickness of the walls associated with physiological remodeling of the heart is characteristic.[19,23,24]

Currently, there is evidence that among patients, although there is some evidence that patients who are carriers of pathogenic or pathogenic sarcomeric genes have a worse prognosis than those with gene-negative genes, and multiple mutations cause the severity of the disease.[25,26,27] The role of molecular genetic testing in athletes with HCMP usually does not affect medical recommendations regarding the type or intensity of physical exercise and sports.[22,28]

Dilated cardiomyopathy - is a phenotypic expression of a sports heart, which is included in the differential diagnosis with dilated cardiomyopathy (DCMP), recognized as the cause of SCD in young people.[3,4,29] In the presence of borderline systolic LV dysfunction associated with other pathological changes, it is necessary to carry out differential diagnosis of physiological remodeling of LV and DCMP, more than 60 genes are associated with DCMP.[9,30,31] Familial DCMP is genetically determined in 55% of cases[32,33], non–familial - 11-26%.[33,34]

The phenotypic expression of genetic DCMP may depend on environmental factors, while specific genotypes, such as defects in the lamin A/C *(LMNA)* and filamin C *(FLNC)* genes, make the disease more susceptible to the harmful effects of exercise.[35,36]

Arrhythmogenic cardiomyopathy (ACM) - is a hereditary disease of the heart muscle characterized by fibrous-fat replacement of the myocardium, causing arrhythmic SCD in young athletes.[37,38] Phenotypically, the disease is characterized by frequent damage to the right ventricle[38], biventricular and left-dominant forms may occur.[39,40,41], determining a wide range of phenotypic variants of the disease with parallel damage to both ventricles or predominant LV damage.[37,42,43]

Pathogenic mutations of genes encoding desmosomal proteins are detected in approximately 50% of affected patients.[37,38] Genetic defects causing the levodominant form, in addition to the desmosomal desmoplakin gene (DSP)[40,41], include a number of other genes associated with cardiomyopathy phenotypes, such as DCMP.

Molecular genetic testing is shown to athletes with indices that already meet the phenotypic diagnostic criteria of ACM. After detecting a pathogenic or probably pathogenic variant, cascade genetic screening should be proposed[9,33,38] if it is possible to perform it. Molecular genetic testing is mandatory for the diagnosis of ACLV, because the phenotypic features of LV do not provide sufficient diagnostic specificity. Thus, the indication for molecular genetic testing is the etiological characteristic of an isolated "non-ischemic LV scar", which may represent early/segmental ACLV, simulating cured myocarditis.[15] Molecular genetic testing in ACM also carries prognostic information, predicting a more serious outcome due to the presence of genetic changes and mutations of desmoplakin, filamin-C *(FLNC)* and

phospholambane *(PLB)* genes associated with a worse phenotype and a more unfavorable outcome.[27]

Physical exercise is one of the most important factors that contribute to the phenotypic expression of ACM and trigger life-threatening disease in ACM. Sports can influence the course of the disease, contributing to the development of phenotypic expression, accelerating the progression of the disease and causing malignant ventricular arrhythmias.[18]

Sinus node diseases and atrioventricular blockages - it is often found in athletes. Intense physical activity may also be associated with atrioventricular (AV) conduction disorders. AV blockades of the first and second degree of type 1 are considered possible manifestations of a "sports heart". Some clinical forms of sinus node disease and AV conduction disorders may have a genetic basis.[21], lesions of both nodes are most common, which is also genetically determined. This is associated with the coding of sodium channel proteins, as well as calcium channels and proteins regulating calcium transport.[34] Molecular genetic testing can be recommended for athletes with pathological impulse formation and AV conduction disorders, a positive family history of early bradyarrhythmias, AV block or unexplained SCD.

Trabecular left ventricle (TLV) – It is characterized by a "non-compact" layer of the trabecular myocardium and a "compact" layer of smaller thickness. Numerous imaging criteria have been proposed for the diagnosis of TLV, the most common of which is the Petersen index with a ratio of "non-compact"/"compact" layer with a magnetic resonance of the heart >2.3.[30] In athletes, these conditions may represent a benign process that does not require additional diagnostic studies.[40,44] This pathology is inherited by autosomal dominant type, with variable penetrance and high intrafamily variability of phenotypic expression, sometimes autosomal recessive linked to the X-chromosome and mitochondrial (maternal) type of inheritance. With isolated TLV with normal LV function and without a family history, molecular genetic studies may not be carried out.[35]

Long QT syndrome - clinically characterized by prolongation of the QT interval on the surface electrocardiogram (ECG) and a tendency to life-threatening arrhythmias, QT 460-480ms, this is the norm in athletes.[1] In the presence of an extended QT interval, a two-phase or serrated T wave is recorded; with Holter monitoring in 12 leads, a change in repolarization, especially at night with fluctuations in the T wave; in anamnesis, cardiac arrest or fainting associated with physical or emotional stress; QT adaptation during exercise is impaired and QT exceeds 480 ms by 4-th minute of recovery.[6,16]

Prolonged QT syndrome is a hereditary heart disease, in which it is necessary to conduct a molecular genetic analysis with a diagnostic value of 80-85%, as well as prognostic and therapeutic prognoses. Sometimes an intensive training process can cause a change in the ECG with an elongation of QT, which can cause a diagnostic error, since a decrease in the load can normalize the ECG, and a change in QT may be associated with a genetic predisposition of the heart muscle to stretch as a result of increased loads.[42] In such conditions, athletes must necessarily undergo a molecular genetic examination to verify and make a final diagnosis, since an incorrect diagnosis of LQTS can have psychological consequences for athletes, leading to a tragic outcome.

Brugada Syndrome (SB) - genetic cardiovascular disease with the risk of sudden cardiac death in young and middle-aged people. Screening of family members of victims with SCD with a normal heart during pathoanatomic examination allows diagnosing SB in 25-30% of cases.[4,39] The diagnostic picture of the ECG in SB is characterized by the rise of the ST segment in the form of an arc, followed by a negative T wave in the right precardial leads (type 1 ECG); the saddle-back patterns (type 2 and 3) are not diagnostic.[6,46] ECG anomalies are usually "dynamic", i.e., they change over time and may sometimes disappear with complete normalization of the ECG.[27] Increased vagus nerve tone, high body temperature, medications or hypokalemia may contribute to the appearance/deterioration of repolarization disorders.[6,47] When the ECG pattern of the SB is not diagnostic, pharmacological provocation with sodium channel blockers is required to make an accurate diagnosis, which make it possible to identify the pattern in affected individuals.[7,38] Since life-threatening arrhythmias usually occur at rest (or during sleep), and not during exercise, SB is usually considered an unlikely cause of sudden cardiac death in athletes. Recognized risk factors for SB include a family history of SCD, syncope, spontaneous type 1 ECG, and even more discussed inducibility with programmed ventricular stimulation; risk stratification scales have also been developed.[38] Mutations of the gene encoding the alpha subunit of the sodium potential dependent channel (SCN5A), the only one definitively associated with SB[7], were associated with an increased risk of arrhythmia. Since molecular genetic testing in affected patients has a low diagnostic value (below 30%), in athletes it is indicated only when phenotypic diagnostic criteria are met or if there is a known mutation causing the disease in the family.

Collagenopathy. It is extremely important to exclude the presence of connective tissue disease or non-syndromic genetic etiology in persons with: 1) phenotypic clinical characteristics; 2) aortic dissection or aneurysm in a family or personal history, especially at a young age (<50 years), with or without recognizable syndromic signs and without a history of hypertension. The most well-known autosomal dominant connective tissue syndrome is Marfan syndrome, which is caused by hereditary or, in 25% of cases, pathogenic de novo variants in FBN1 encoding fibrillin-1, an extracellular

matrix protein that provides the structure and elasticity of the aortic wall. Many phenotypic features of Marfan syndrome also characterize Loes-Dietz syndrome, an autosomal dominant disease caused by mutations in at least 5 genes that contribute to the signaling pathway of transforming growth factor beta (TGFß).[48]

As the analysis of the literature has shown, molecular genetic testing is becoming promising and accessible for assessing the CVS of athletes, with the help of which it is possible to confirm the clinical diagnosis and hereditary nature of diseases, as well as to conduct differential diagnosis, CMR and adaptive changes in the heart of athletes. However, it should be noted that sports doctors and cardiologists should take into account the limitations of genotyping, paying special attention to the interpretation of test results, so molecular genetic testing of an athlete can confirm a clinical diagnosis. The development of molecular genetic studies and their introduction into sports medicine in the future will allow identifying pathogenic mutations, with the help of which it is possible to carry out differential diagnosis, or confirm a clinical diagnosis among athletes with hereditary CVD.

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